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A Case Report of North American Blastomycosis with Review of the Literature

HANS-JOACHIM WIGGER, M.D.*

INTRODUCTION[6, 11, 13, 14, 17–19, 21]

North American blastomycosis, or Gilchrist's disease, is a chronic granulomatous infectious disease produced by the hyphomycete, *Blastomyces dermatitidis*. It was first described in 1894 by Gilchrist, who together with Stokes also discovered the pathogenic organism in 1898. In 1902 Walker and Montgomery described the systemic form of the disease. Because of the difficulty of making the diagnosis of North American blastomycosis, confusion with other disease—all caused by a similar single budding organism—was quite frequent. In 1907, Hektoen described 13 more cases of generalized infection with *B. dermatitidis* and reviewed the literature up to that date. Since then many comprehensive reviews of the literature and large numbers of cases have been added. Following the first therapeutic trials of propamidine and stilbamidine numerous cases have been reported in which the aromatic diamidines were used with or without success. Smith has presented an extensive study of the immunologic types of the disease. A new concept of pathogenesis was propagated by Schwartz and Baum stipulating that most infections with *B. dermatitidis* are primary pulmonic.

According to Martin and Smith, 98 per cent of 340 proven cases of North American blastomycosis originated in the United States. Of these, the majority occur in the southeastern and midwestern states; sporadic cases, however, have been reported from all of the remaining states and Canada. Case reports from practically all other continents have appeared in the literature during the past decade, and the density of intercontinental traffic increases the possibility that individuals from endemic areas may develop the disease in other countries.

South American blastomycosis, also known as paracoccidioidal gran-

* Junior Associate Staff, Assistant Pathologist, Department of Laboratories, Children's Hospital.

uloma, is a disease similar to North American blastomycosis. However, the causative organism, *Blastomyces braziliensis*, in the tissues is characterized by the presence of multiple buds, and lesions of lymph nodes and mucous membranes are prominent. The gastrointestinal tract is much more frequently involved than in the North American variety.

CASE REPORT†

This 7 year old Negro girl, who was admitted to Children's Hospital May 29, 1955, had been in relatively good health until three months prior to admission, when she developed "pneumonia" which was treated by the private physician with penicillin, streptomycin, and oxytetracycline. Most of the symptoms subsided after this treatment, but a dry, nonproductive cough, poor appetite, and night sweats persisted up until the time of admission. One month prior to admission a lump appeared on her left hand and was incised and drained; bacteriological examination of the purulent material was not made. The incision did not heal and purulent discharge continued to drain from it. Nine days prior to admission the patient contracted measles from which she recovered uneventfully. Three days prior to admission she developed a fever and began coughing up large amounts of greenish sputum; this was accompanied by vomiting, abdominal pain and lethargy.

According to past history the patient had had chickenpox and whooping cough without complications. Her parents and five siblings were living and well. No family disease history was reported. A few months prior to admission she had paid a visit to her grandparents in South Carolina.

Physical examination on admission to the hospital revealed a well developed and well nourished Negro girl who appeared to be acutely ill and in moderate respiratory distress. Her rectal temperature was 102° F., her pulse rate 140 per minute, and respiratory rate 36 per minute. Her weight was 42 pounds. The abnormal physical findings included dullness to percussion, diminished breath sounds, and a few moist rales in the lower two thirds of the right posterior lung. A small healing ulceration on the thenar region of the right hand was present. The initial laboratory investigation showed a normal urinalysis, a blood hemoglobin of 9.4 Gm. per 100 ml. and a white blood count of 28,600 per cu. mm. with a shift to the left in the differential count. X-ray of the chest revealed a homogeneous density over the lower half of the right chest displacing the heart somewhat to the left. Bilateral scattered calcifications were noted in the pulmonary parenchyma (fig. 1).

In the beginning the diagnostic impression was right lower lobe pneumonia with possible empyema. The patient was treated with penicillin, chlortetracycline, and erythromycin. Shortly after admission a thoracocentesis was done but no fluid obtained. A PPD skin test for tuberculosis was negative and remained negative throughout the hospitalization. The fever subsided gradually within 12 days after admission. At that time the patient appeared markedly improved, although the physical and roentgen findings did not change.

A histoplasmin skin test was initially negative but became weakly positive two weeks later. In three gastric washings no pathogenic organisms were grown; in one

† This case has previously been reported by J. W. Oberman and E. F. Gilbert as "The Toxicity of 2-Hydroxystilbamidine: Probable Fatal Toxic Reaction During Treatment of Blastomycosis," published in the Annals of Internal Medicine, volume 48: (1958), page 1401.

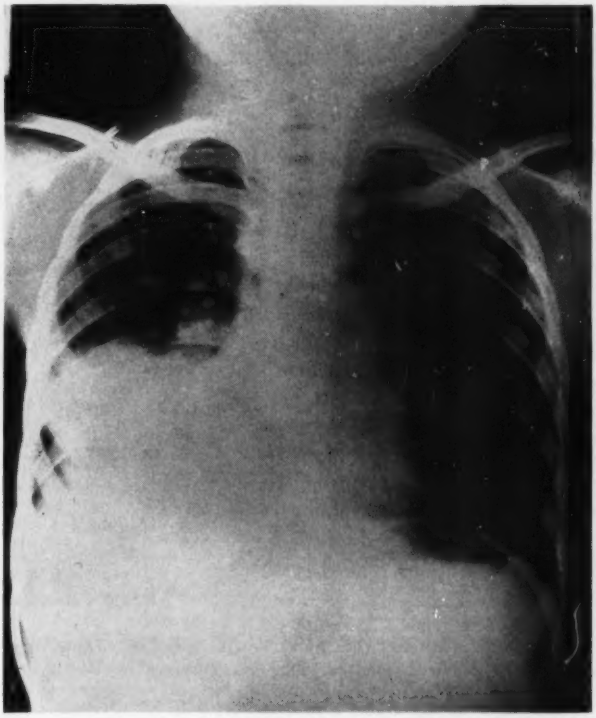

FIG. 1. Postero-antero view of the chest showing a homogeneous density over the lower half of the right chest. The heart is somewhat displaced to the left. There are scattered pulmonary calcifications.

of them *Candida albicans* was isolated. A scalene node biopsy showed chronic inflammatory changes. A barium swallow revealed no pathology. On bronchoscopy no lesions or other abnormalities were seen, but a bronchogram demonstrated a filling defect of the right middle and lower lobe bronchi. A repeat roentgen film of the chest revealed a localized area of pneumothorax in the lower right chest. On June 27, after a blood transfusion, a right exploratory thoracotomy was performed. The right pleural space was completely obliterated and the lower two thirds of the right lung showed a generalized infiltration. The lymph nodes of the right hilum were moderately enlarged. Because of the extension of the infiltrative process over two lobes, a complete removal of the involved portions was not attempted, and only a wedge biopsy and one lymph node were removed for examination. The patient tolerated the procedure well.

Microscopic examination of the biopsy tissue showed numerous granulomatous lesions containing organisms morphologically resembling blastomycetes (fig. 2). From cultures of this tissue on Sabouraud's dextrose and Littman's oxgall agar *Blasto-*

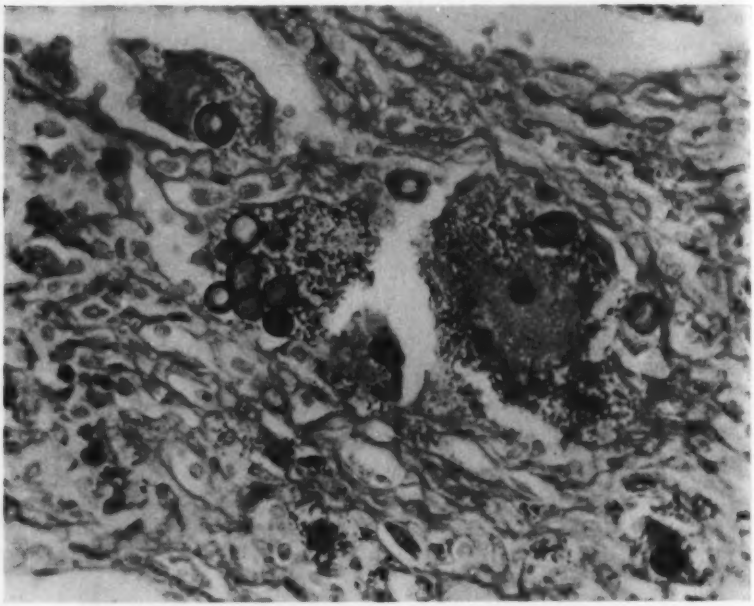

FIG. 2. Microscopic section of the lungs, showing giant cells containing numerous *Blastomyces dermatitidis* organisms. × 500. Gomori stain.

myces dermatitidis was isolated. Complement fixation tests performed at the National Institutes of Health gave negative reactions for histoplasmosis and coccidioidomycosis, but a titer of 1:32 for Blastomyces antibodies.

With the diagnosis of North American blastomycosis thus substantiated, therapy was started with 2-hydroxystilbamidine on July 16. The dosage (225 mg. daily) had to be decreased temporarily because of side reactions of nausea, headache and fever, but was increased again on August 8 to twice the original daily dose. The total dose of 2-hydroxystilbamidine given over a 36 day period was 7.65 Gm. No more side reactions were encountered except that the patient was intermittently anoretic and occasionally vomited. On August 22 the patient suddenly had a grand mal seizure. The therapy was stopped and the patient placed on intravenous fluids and intravenous barbiturates. She regained consciousness and began taking fluids orally, but the convulsions recurred and barbiturates had to be administered almost continuously for their control.

On August 24, the white blood count was 11,300 per cu. mm.; most of these were polymorphonuclear leukocytes. Serum potassium, sodium, calcium, and chlorides were below normal levels. The rectal temperature rose to 103° F. and the liver became palpable. On the following day, the urine sugar was 3+ positive, the acetone 2+ positive, and albumin 200 mg. per 100 ml.; the urinary sediment contained granular casts. A cisternal puncture revealed slightly bloody fluid containing 20,000 red blood

cells and 52 white blood cells, of which 86 per cent were polymorphonuclears and 14 per cent lymphocytes. The protein content was 30 mg. per 100 ml. Tests of liver function included cephalin flocculation 4+, thymol turbidity 9 units, and a total bilirubin 1.4 mg. per 100 ml. (0.9 direct, 0.5 indirect). Total serum protein was 5.7 Gm. per 100 ml. and the albumin-globulin ratio 1.9/1.0. The convulsions became more frequent and difficult to control, and the patient expired August 26.

Postmortem examination was performed three hours after death. Organs demonstrating the most marked pathology were the lungs, liver and adrenal glands, and to a lesser extent, kidneys, heart, spleen, cerebral cortex and bone marrow. On gross examination the inferior surface of the right lower lung lobe was found to be densely adherent to the diaphragm. The pleural surfaces of both lungs were studded with raised, firm, gray, well circumscribed nodules averaging 0.3 cm. in diameter. The right middle and lower lobe bronchi were surrounded by dense grayish red pulmonary tissue which on section revealed irregularly circumscribed gray firm areas measuring up to 3 cm. in diameter. Section of the right and left upper lobes demonstrated numerous small gray miliary lesions. The left lower lobe was not involved. The tracheobronchial and retromediastinal lymph nodes were pinkish gray and averaged 2 cm. in diameter. These were hard, partially caseous, and calcified on section. The liver weighed 764 Gm. (normal 680 Gm.). Its surface was light yellow and smooth. On section it appeared markedly yellow, and the portal pattern was indistinct.

On microscopic examination there was irregular thickening of the pleura. The pulmonary parenchyma was distorted by multiple granulomatous lesions containing giant cells of the Langhans type and double-walled structures several times the diameter of erythrocytes. These latter structures appeared to be transparent with routine hematoxylin and eosin staining, and were reddish lilac in color with the Gridley stain; they were identified as *B. dermatitidis* organisms. There were also many areas of dense fibrosis, calcification and acute inflammatory exudate scattered throughout the entire right lung and the left upper lobe. In other sections there were large areas of bronchopneumonia and emphysema. (Description according to the review of the microscopic sections of the lungs by Dr. L. E. Zimmerman of the Armed Forces Institute of Pathology.) In addition to blastomyces organisms in the pulmonary parenchyma, some small areas in the lungs and hilar lymph nodes were observed to contain focal, discrete, encapsulated fibrocaseous granulomas showing organisms resembling *Histoplasma capsulatum*.

The liver demonstrated a severe degree of fatty infiltration and degeneration, as evidenced by widespread vacuolation. This process also involved the tubules of the kidney, but to a lesser degree. A striking feature was the presence of small dense basophilic granules in the cytoplasm and the nuclei of hepatic cells, the tubular epithelium of the proximal convoluted tubules and the cortical cells of the adrenal gland. These granules were also seen in smaller amounts in the myocardium and occasionally in ganglion cells of the central cerebral cortex and reticulum cells of the spleen and bone marrow. Exposure to fluorescent light caused strong fluorescence of the tissues. These granules were thought to be 2-hydroxystilbamidine, toxicity to which was believed to have caused death due to hepatic failure.

DISCUSSION

Epidemiology and Pathogenesis[4–9, 12, 18]

Although most of the systemic mycoses have been isolated from nature, there is no conclusive evidence of an infective saprophytic form of

Blastomyces dermatitidis. Emmons, however, successfully cultured *B. dermatitidis* in sterilized soil in the laboratory; in view of this, the soil is suspected to be the natural reservoir of the organism. Another reservoir is believed to be domesticated animals, as natural infection in both its generalized and pulmonary form has been observed in dogs and horses. No direct natural transmission from man to man has yet been proved. A few isolated cases have been described where accidental mechanical inoculation has occurred through a break in the skin in personnel handling the organism or infected material. Schwartz and Baum found that close contact with diseased persons did not give rise to positive blastomycin skin reactions. The same authors, in reviewing 60 cases, suggested that practically all cases of North American blastomycosis are pulmonary in origin and that the skin lesions in these cases are secondary to a dormant or active infection of systemic nature. Primary cutaneous North American blastomycosis demonstrates a typical primary complex consisting of a primary skin lesion with an ascending nontender lymphangitis and regional lymphadenitis. The role of trauma has been overemphasized. The same authors found that involvement of the lungs is already present in many patients with so-called primary cutaneous North American blastomycosis, and the rapid simultaneous development of several skin lesions speaks against a primary cutaneous form. It is proposed that infection occurs by inhalation, as in coccidioidomycosis and histoplasmosis, although no proof of this manner of transmission exists. There is likewise little knowledge to shed light on whether or not North American blastomycosis follows the epidemiologic pattern of histoplasmosis and coccidioidomycosis. Unfortunately the proof of the presence of widespread mild infections depends on skin test surveys. The only verified epidemic investigated epidemiologically is the one in Grifton, Pitt County, North Carolina, reported by Harris and his group. The sudden appearance of 10 pulmonary cases induced this investigation. A survey of the town population revealed a number of persons with positive blastomycin skin tests and negative histoplasmin skin tests. No other case of North American blastomycosis was encountered and the source of the epidemic could not be determined.

The findings of Schwartz and Baum indicate that lymphatic, hematogenous, and intracanalicular spread are possible. Lymphatic spread is a rare means of propagation of the disease and apparently occurs only in primary cutaneous North American blastomycosis. It is most likely that in the majority of cases dissemination of the organism occurs by the blood stream. Whether or not the hematogenous infection originates in infected lymph nodes located close to the entrance of lymph vessels into veins, as Ghon, Kudlich and Schmiedl have demonstrated in tuberculosis, is not

known. The presence of lymphadenitis due to *B. dermatitidis*, however, strongly suggests the lympho-hematic spread. In the advanced state of systemic North American blastomycosis direct invasion of capillaries in granulomatous lesions might be possible. Schwartz and Baum have repeatedly observed blastomycetes in arteries and veins. The third form, intracanalicular spread, seems to be common in the lungs. As a matter of fact, bronchial involvement was a constant feature observed following intravenous and intraperitoneal injection of the organism into mice. The exudate containing *B. dermatitidis* reached the bronchial tree by way of extension from alveolar inflammatory foci or through an ulceration in the bronchi. Other organs with preformed channels such as kidney, testis, epididymis, or prostate may demonstrate the same type of dissemination. A rare but indeed observed form of propagation is the spread along perineural and endoneural spaces. All individuals with pulmonary North American blastomycosis have pleural manifestations.

Pathological Anatomy[2, 6, 9, 18, 22]

Grossly the involved lungs are extremely heavy and show either small pneumonic or confluent foci, miliary nodules or scars. Cavities usually do not develop but there may be large exudative lesions containing necrotic foci. Organizing, adhesive pleuritis, ulceration into the small bronchi with tenacious mucopurulent exudate and regional lymphadenopathy were frequently observed by Schwartz and Baum.

The exudative pneumonic type, without granuloma formation, is represented by neutrophilic infiltrations containing frequent to numerous *B. dermatitidis* organisms. Alveolar destruction and focal necrosis are usually present but never to such an extent as in tuberculous caseous necrosis. The granulomatous lung lesions consist of tubercle-like epithelioid cell foci with many giant cells. Yeast cells are less frequently detected than in the exudative form and are usually within giant cells. Both exudative and granulomatous lesions may occur in the same lung. Old pulmonary lesions are observed to be either diffusely or nodular fibrotic; the latter cannot be distinguished from the corresponding lesions of tuberculosis or healed sarcoidosis. Calcification is rarely noted. In healed lesions of North American blastomycosis there is a marked tendency to hyalinization.

Bronchial lesions are caused by extension from the involved pulmonary parenchyma. Moderate numbers of yeast cells can be detected in the bronchial wall and the mucopurulent bronchial exudate.

Caseation of lymph nodes has not yet been found. This may be due partly to the fact that a primary pulmonary complex analogous to that seen in tuberculosis has not been established in North American blastomycosis. Lymph nodes usually show occasional yeast cells (mostly in

the peripheral sinuses), tubercles, focal necrosis, fibrosis and rarely calcification or ossification.

The initial growth of the skin lesion is slow, but sudden regional extension may occur and microabscesses may develop on the elevated border of the lesion. With further growth the central portion of the lesion becomes necrotic and ulcerates, and later forms a scar with atrophy of the skin. Microscopically there are hyperkeratosis, pseudoepitheliomatous squamous cell hyperplasia, and microabscesses. There does not seem to be any difference between the histologic appearance of the primary and secondary lesions in the patient with systemic disease.

Contrary to what is seen in South American blastomycosis, the digestive tract shows surprisingly little involvement; the reason for this is obscure. Practically all organs have been noted to be involved with *B. dermatitidis*. North American blastomycosis of the genitourinary tract is almost certainly hematogenous in origin; local spread occurs intracanalicularly. Lesions are found in the following sequence according to frequency: kidney, prostate, testis, epididymis, seminal vesicles, and bladder. Genitourinary tract obstruction due to the disease has also been observed. North American blastomycosis of the central nervous system occurs either in a diffuse form resembling an acute infectious process or in a localized form clinically simulating a space-occupying lesion and pathologically simulating a tuberculoma. The bone lesions in North American blastomycosis are essentially destructive, giving rise to abscess formation, separation of sequestra, and development of chronic discharging sinuses.

Clinical Manifestations[3, 4, 6, 15, 18]

Most cases of North American blastomycosis have been reported in individuals between 30 and 50 years of age, but the disease has been observed in all age groups, from a 5 month old infant to an 84 year old person. A definite sex relationship has been found; North American blastomycosis is from 5 to 15 times more frequent in men than in women. This has been assumed to be due to the fact that men are more exposed to dust, soil and wood. There is, however, no proof of a definite occupational relationship to the disease. A racial immunity does not seem to exist.

Most authors have divided the manifestations of North American blastomycosis into two forms, the localized cutaneous form and the disseminated or systemic form. This division formerly seemed to be well justified, since the two types were thought to be different in their clinical course, prognosis and response to therapy. They were also thought to be due to a different modus of infection, a theory which was to some extent disproved by Schwartz and Baum, who stressed the similarity of North American blastomycosis to coccidioidomycosis. The skin lesion first appears

as a papulopustule located primarily on exposed areas such as the hands, feet, wrists, ankles, and face. Palms, soles and scalp are rarely affected. The primary lesion enlarges slowly to a verrucous, ulcerative granuloma, a process which may take months or even years. If one tries to remove the crusts covering the ulceration, bleeding occurs. The crusts are produced by a seropurulent discharge from the irregular, wartlike surface of the granuloma. The well-demarcated and elevated border of the granuloma is violet in color and contains miliary abscesses. As the lesion extends peripherally the center slowly heals with formation of an atrophic scar. This healing process may not be complete, however, and miliary abscesses may persist and induce recurrences of the lesion. In most cases of primary cutaneous North American blastomycosis there will be an ascending nontender lymphangitis with regional lymphadenopathy. According to Schwartz and Baum, however, the skin lesions are secondary. These authors claim that the primary cutaneous form of North American blastomycosis is quite rare and that the skin lesions in most patients are secondary to a dormant or active infection elsewhere; this is thought to be most frequently a primary pulmonary infection. In the secondary form of cutaneous infection, regional lymphangitis and lymphadenopathy are unusual. Multiple lesions in close proximity may coalesce and form serpiginous contours. The usual size of the cutaneous granuloma is 3 to 4 inches in diameter, but some may extend up to 12 inches and involve part of the trunk or a whole extremity. Subjective symptoms are either absent or at least very mild; pruritus is often noted. If systemic involvement is absent, the general health of the patient is not impaired. The clinical course of the primary cutaneous form is chronic, with long periods of remissions and exacerbation.

The systemic form can involve any organ, but most frequently begins in the pulmonary tract. There is no syndrome which could be called characteristic of systemic North American blastomycosis. The presenting signs depend on the organ involved and on the extent of the involvement. Most frequently involved are the lungs, skin, subcutaneous tissues and bones. Pulmonary involvement is marked by respiratory symptoms such as cough, expectoration, and hemoptysis. The onset is usually insidious except in the case of acute, fulminating blastomycotic pneumonia which gives rise to symptoms such as chills, fever, productive cough, chest pain, hemoptysis, weight loss, night sweats, and dyspnea. The infection may assume a miliary form with abscess and sinus formation following. Depending on the nature and the extent of the lesion, one may find rales, increased vocal fremitus, and decreased breath sounds.

As the pulmonary process progresses, dissemination to other organs may occur. But, according to Schwartz and Baum, dissemination is also possible

when the primary focus is in the process of involution. In some cases, secondary skin lesions may develop on unexposed parts of the body, appearing first as deep, painful nodules with a tendency to break through the skin and resemble the previously described cutaneous lesions. Involvement of the skeletal system is not uncommon (in up to 50 per cent of cases). The symptoms are those of osteomyelitis, periostitis and septic arthritis. Pain and loss of function are the most outstanding symptoms. The ribs, vertebrae, skull and elbow joints are most frequently affected. Destruction and collapse of vertebrae may occur as in tuberculosis. When present in the long bones, the disease often spreads into the adjacent joints.

Involvement of the urinary tract causes pyuria, hematuria, dysuria, prostatic enlargement, and urinary retention. The female genitalia are rarely involved. Noojin and Praytor reported the case of a woman who developed North American blastomycosis in the second trimester of pregnancy; the infant was normal and unaffected.

North American blastomycosis of the central nervous system is quite uncommon. The symptoms depend on the location and the nature of the lesion which may cause focal or diffuse meningitis and single or multiple abscesses. Progressive cases present the appearance of any chronic, generalized, debilitating infection with inanition, anemia and cachexia. Involvement of the gastrointestinal tract, adrenals, thyroid, eyes and larynx is extremely rare.

The laboratory findings are nonspecific. There is usually a leukocytosis with a preponderance of polymorphonuclears which will be more pronounced in the presence of a superimposed bacterial infection. The erythrocyte sedimentation rate is always elevated and seems to correlate well with the activity of the disease. As the disease progresses, a hypochromic anemia develops. The bone marrow in some cases has shown an unusually high number of plasma cells. Blood cultures are most frequently negative as have been the reported cultures of bone marrow aspirations.

Diagnosis[4–6, 14, 15, 18, 20, 22]

Since the clinical history and physical findings are so nonspecific, only a presumptive diagnosis can be made unless the demonstration and identification of the pathogenic organism can be made. Direct microscopic examination of infected fresh material such as pus, sputum, urine, cerebrospinal fluid, scrapings from skin lesions, prostatic fluid and effusions are easily done by wet mounting of the specimens or their sediments on glass slides with 10 per cent potassium hydroxide. Collection of these specimens should be standard procedure. The cover slip preparations are examined under the microscope with subdued light to bring out the refractivity of

the thick, double contoured walls of *B. dermatitidis*. Confirmation of the diagnosis by culture is always desirable. The specimens are planted on Sabouraud's dextrose agar and incubated at room temperature where the organism should grow in the mycelial phase. On blood or brain heart infusion agar the yeast phase will grow at 37° C. Growth of contaminants can be suppressed by adding streptomycin and penicillin to the media. For intraperitoneal or intravenous animal inoculation the mouse is the most suitable. However, one usually does not need to employ this method.

Culture and histopathologic examination of biopsy material are very valuable diagnostic procedures. Skin biopsies from the active border of the granuloma, bronchoscopy, thoracotomy, prostatectomy, and needle aspiration of the liver or lung have been utilized to obtain tissue for these purposes. For screening procedures and in mild or obscure cases the skin test is usually helpful. The cutaneous hypersensitivity of a patient with North American blastomycosis is demonstrated by intradermal injection of 0.1 ml. of a standardized antigen, which is either a vaccine of the killed yeast-phase organism or a culture filtrate called blastomycin. Dilutions of 1:10 to 1:100,000 are employed. The technique of administration, interpretation and significance is similar to that of the tuberculin test. In the average patient it is customary to begin with a 1:1000 dilution of the commercially available blastomycin. As in other skin tests, a positive result, i.e., erythema with central induration after 24 to 48 hours, is indicative of a past or present infection. The results obtained with blastomycin skin tests are not as consistent as those in tuberculosis, coccidioidomycosis and histoplasmosis.

It has been observed that the test is generally negative in the early stages of the disease, in mild, localized cutaneous forms, and in the overwhelming or terminal phase. Confusion may arise from the occurrence of cross reactions with antigens of *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces braziliensis*; this suggests that there is a common antigen. Therefore, the blastomycin skin test should always be performed simultaneously with coccidioidin and histoplasmin skin tests. Only after investigation of a large series of cases of North American blastomycosis will it be possible to establish the significance of the blastomycin skin test.

Like the skin test, the complement fixation test gives only presumptive evidence. This test is negative in early, mild or localized cutaneous North American blastomycosis; the titer increases with progression of the disease and remains high throughout the terminal stage. Therefore, a high complement fixation test with a negative skin test indicates a poor prognosis. A passive transfer of these complement fixing antibodies from mother to child has been demonstrated. Cross reactions with sera from patients with histoplasmosis, coccidioidomycosis or blastomycosis unfortunately do occur

and make it necessary to perform all three complement fixation tests simultaneously. The serum, however, will usually show a higher titer of antibodies to the disease actually present.

The clinical manifestations and, therefore, the differential diagnosis depend largely upon the signs and symptoms produced by the most extensively involved organ or organs. The cutaneous lesions may be confused with the lesions of conditions such as lupus vulgaris, tuberculosis verracosa cutis, the nodulo-ulcerative syphilide, and gumma. They may also be mistaken for lesions of other fungus infections such as sporotrichosis, coccidioidomycosis, paracoccidioidomycosis, chromoblastomycosis, actinomycosis, cryptococcosis, and trichophytosis. Granuloma inguinale, anthrax, tularemia, pyoderma vegetans, yaws, cutaneous leishmaniasis, mycosis fungoides, and squamous and basal cell carcinoma must also be considered. The primary cutaneous type with regional lymphadenopathy must be differentiated from other chancriform diseases such as inoculation tuberculosis, syphilis, yaws, American leishmaniasis, sporotrichosis, tularemia, and cat scratch fever. The symptoms of the initial stage of the pulmonary form of North American blastomycosis may resemble such diseases as the common cold, influenza, or pneumonia. The manifestations of the more advanced form may be simulated by other systemic diseases such as tuberculosis, syphilis, primary and metastatic malignancies, pulmonary abscess, bronchiectasis, bacterial pneumonia, sarcoid, lymphoma, pneumoconiosis, multiple myeloma, tularemia, septicemia, osteomyelitis, histoplasmosis, coccidioidomycosis, South American blastomycosis, sporotrichosis, cryptococcosis, candidiasis and actinomycosis. It should also be kept in mind that simultaneous involvement of the lungs with other diseases such as tuberculosis, carcinoma, sarcoidosis, and histoplasmosis may occur.

In untreated cases of primary cutaneous North American blastomycosis the prognosis for life expectancy is good; conversion into the systemic form rarely occurs. The chronicity, however, is quite marked, and the lesion may recur for many years. Wilson and associates are inclined to believe that there is a tendency toward spontaneous healing. Whether the secondary cutaneous lesions heal or spread depends largely on the course of the systemic disease which has a high mortality rate. Recently, however, evidence has been presented that spontaneous healing of the systemic form of North American blastomycosis may occur. This contention remains to be confirmed in larger numbers of patients.

Treatment[1, 4, 6, 10, 16, 18]

As with other diseases, the discouraging results with available therapy are evidenced by a multitude of procedures and drugs employed to combat

the disease. Since it was suggested by Gilchrist, iodide has been used extensively in the treatment of cutaneous lesions. A mixture of equal parts of ammonium, sodium, and potassium iodide was best tolerated. Surgical procedures are also of value in the cutaneous form: complete excision, with or without skin graft, cauterization, electro-coagulation, cryotherapy or currettage may be employed. The risk of dissemination with these procedures should also be borne in mind. Roentgen therapy has been helpful in eradicating small early lesions. Combination of all these therapeutic aids has produced the best results. In the systemic form of North American blastomycosis, iodide treatment produces only temporary improvement, if any. In some instances the disease has been adversely affected. Other agents, such as undecylenic acid, chlortetracycline, colloidal copper sulfate, ether and penicillin, have been reported as successful.

A revolution in the treatment of North American blastomycosis was brought about with the introduction of the aromatic diamidines. Propamidine and, later, stilbamidine and 2-hydroxystilbamidine have brought about remarkable improvement and apparent cures in a significant number of cases. Failures, especially in the form of recurrences, and toxicity of the drugs have diminished the value of the diamidines. Assistance may come from the growing number of antifungal antibiotics such as rimocidin, fradicin, mycostatin, and amphotericin. Surgical procedures are of certain value in specific instances: incision and drainage of large pockets of pus; prostatectomy for relief of urinary obstruction due to prostatic involvement; excision of laryngeal, prostatic and uterine lesions. Excision of isolated secondary skin lesions with the purpose of arresting the primary focus has been attempted. Localized pulmonary foci, when present as the only lesions, can be resected with success. Unfortunately, the pulmonary foci are usually diffuse and multiple or too extensive, and thus not amenable to surgery. These many therapeutic modalities should not result in the overlooking of the importance of general supportive treatment such as bed rest, good nutrition and nursing care which are as necessary as in any other severe debilitating infection.

SUMMARY

A fatal case of North American blastomycosis is presented and the American literature reviewed. The epidemiological pattern which the disease follows is largely unknown. The pathogenesis follows mainly that of other infectious granulomatous diseases; lymphatic spread is almost completely limited to the primary cutaneous form, while lympho-hematic and hematogenous dissemination predominate; canalicular spread is mainly observed in the lungs. The most typical pathologic-anatomical response of

the tissue to the invasion of the *Blastomyces dermatitidis* is granulomatous, with tubercle-like lesions containing mostly epithelioid cells, giant cells, and, to a lesser degree, plasma cells, lymphocytes and polymorphonuclear leukocytes. The response may in the beginning be primarily exudative and later become granulomatous, and show various combinations of suppuration, necrosis, fibrosis, calcification and ossification. Exudative lesions containing many neutrophiles and abscesses prevail in the acute stages, while lymphocytic infiltration and fibrosis predominate in the chronic phase. Practically all organs may be involved. Since the most frequently involved organs are the lungs, the skin and the bones, symptoms deriving from the disease of these organs will make up the main clinical manifestations. Laboratory findings are nonspecific, and culture and histopathological examination are necessary to confirm the diagnosis. The results obtained with blastomycin skin tests are not as consistent as those in tuberculosis, coccidioidomycosis, and histoplasmosis. Here, as well as in the complement fixation reaction, cross reactions with other fungal infections may occur.

The prognosis for life expectancy in the primary cutaneous form is good, but the systemic form has a high mortality rate. A large variety of drugs have been reported to combat the disease successfully in individual cases, but it was not until the advent of the aromatic diamidines and antifungal antibiotics that the therapeutic outlook was improved considerably.

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The Adolescent: A Concept of Medical Care

Felix P. Heald, M.D.*

Our concept of care for the adolescent has certain broad implications for the care of younger patients, and hopefully some of the principles that are being evolved in handling this age group will extend to young children. Is this concentrated effort for this age group necessary and worth the considerable amount of effort and money going into adolescent units? This can be answered somewhat simply by quoting from an editorial in the New England Journal of Medicine in 1953:[1]

> A neglected field of medicine has been that of adolescence. The explanation is simple. Until recently the pediatrician has been preoccupied with premature

* Academic Staff, Director of Adolescent Medicine, Children's Hospital; Assistant Professor of Pediatrics, Georgetown University School of Medicine.

babies, transfusions, feeding problems, and running ears; the internist has also been busy with fields of adulthood and advancing age and has still to come to the period of adolescence. Yet, the field is particularly important, marking as it does the transition from girl to woman and from boy to man.

How do we define adolescence? The Oxford Universal Dictionary gives two interesting definitions. The first is, "Process or condition of growing up, or the growing up age," and the second, "The period between childhood and maturity extending from ages 12 to 21 years in females, and 14 to 25 years in males." This latter age discrepancy is difficult to understand, either on biologic or emotional grounds. For practical purposes adolescence can be defined as beginning when the adolescent growth spurt has been initiated. Its biologic termination is heralded by the cessation of growth, which occurs between 16 to 18 years in girls and 18 to 20 years in boys.

In whose domain does this age group belong? Is care of the adolescent the province of the pediatrician, the internist, or the general practitioner? It is, of course, the province of all who are interested, and such training centers which have developed, are developing, and will develop, are and should be a synthesis of the medical thinking of the pediatrician, internist, and the many allied specialties, all of whom can focus upon and bring their experience to bear on this age group. Adolescence itself typifies this synthesis, an ever-changing period both physiologically and emotionally of the older child into the adult.

The one advantage the pediatrician has in this regard is his familiarity with the concept of change. If there is one thing characteristic of the adolescent, whether physiological, emotional or otherwise, it is his constant, rapid and often irregular and seemingly irrational change. These seemingly irrational events will become more rational as we have a better understanding of this age group.

The question, "What is different about an adolescent?" might be rephrased, "What is different about an adolescent physiologically?" First, velocity of linear growth is intense; most aspects of the body seem to participate in the adolescent growth spurt, whether it be osseous elements as manifest in height increments, or body fat which decreases by 50 per cent between the ages of 12 and 18 years in boys. In contrast, the adolescent girl appears to increase her total body fat during a similar period. There are two tissues of the body which do not participate in this intense growth spurt: the brain and lymphoid tissue. Present evidence suggests that the amount of lymphoid tissue decreases during adolescence.

There are other aspects of change that characterize adolescents. For example, total body water increases during adolescence although the changes are small and possibly not of clinical importance. Nutrition is of striking importance. Adolescent girls at age twelve or thirteen are eating more, at least in terms of caloric intake, than they do at any period of

life thereafter. With adolescent boys, intake is even more marked; at age sixteen, an average boy's intake is about 1,000 calories higher. This has a great deal of clinical significance in, for example, regulation of the diabetic.

Basal oxygen consumption in adolescent girls reaches its highest point just prior to the menarche; thereafter it seems to decline. It has been the observation of some that in certain girls this high basal oxygen consumption is accompanied by signs of mild and transient hyperthyroidism. In adolescent boys, basal oxygen consumption is higher in absolute values than in girls and rises through adolescence, plateauing at the seventeenth year.

There are obvious complex endocrine changes which occur in both the male and female adolescent. Their integration and relationship to growth and to body composition are only partly understood. Menarche in girls is of signal importance as an event which has much emotional and physiological meaning. The menstrual cycle does not become mature overnight, and we have to think in terms of menarchal age rather than chronological age in evaluating gynecological disorders. At the chronological age of seventeen, for example, there is some evidence that 30 per cent of adolescent girls are still having anovulatory menstrual cycles.[2] In fact, the whole spectrum of the initiation of the menstrual cycle, its relationship to ovulation, and the number of girls who ovulate after a year or two of menstruation is not known.

This much abbreviated discussion of adolescence is only intended to remind all physicians that adolescent physiology differs significantly from the child and the adult. These differences have not been fully documented nor has their impact on diseased states occurring during adolescence been fully understood.

A second and equally important area in which adolescents differ from younger children and adults is in emotional composition. They, of course, basically are a mixture of child and adult, and how much adult or child they are on one day may well differ on the following week: this mixture is a rapidly changing one. In their own clumsy way these adolescents are striving, some mildly, some desperately, for independence, and their drive for independence takes various and often unsuspected avenues. They are trying to separate themselves from family ties, some from family ties that are too strong and difficult for them to break (if indeed they are able to break them at all), and some from ties that barely exist. They are trying to develop a concept of their own identity and worth as individuals, and, in fact, certain emotional disturbances in the adolescent are described as identity crises.[3] An added difficulty for the present-day adolescent is our own society, which in a certain sense tends to discourage the independent and healthy nonconformity of youth.

What are some of the characteristics of adolescents which have clinical

import to physicians? First is their tremendous concern about body growth. This is easy to explain in part, since they, whether they are ready for this change or not, are presented with a new body. They tend to be quite introspective about this; they do a great deal of thinking about their physical self, and often are tremendously concerned about any deviation from the norm. They are concerned particularly about the genital area. A recent example occurred in a typical "all American" boy who was hospitalized for cystoscopy. This procedure was explained to him, and the next day he was asked if he had any questions about cystoscopy. He had two questions. The first was a routine question, and the second one, which he was only able to state with difficulty, was whether cystoscopy would mutilate his genitals. This was not an abnormal response but rather a genuine worry from a perfectly healthy adolescent boy.

A second characteristic to be kept in mind is their fear of being different and the need to conform to their own age group. This is not entirely a product of our culture, but largely a part of their own needs as adolescents. They dislike being too tall or too short. The adolescent girl who has had an early menarche and who at age twelve towers above her classmates, will ask: "Doctor, if I am this tall at age twelve, what will I be at age seventeen?" The short 15 year old boy who is disturbed about not growing up may ask, "Doctor, I get banged up on the football field, and the girls ignore me; will I ever grow up?" This fear of being different is often handled in a way which operates against the physician: it is frequently handled by denial. The boy previously mentioned was ill for two weeks with chills and fever, and completely kept this from everyone. Only when he was so obviously ill did he tell his parents. We hear this story repeated over and over again.

A third characteristic is their previously mentioned need to be independent and to find their own identity. They do not like to be treated as children nor do they like to be treated as adults. They like to be treated and need acceptance really for what they are and not what we would like them to be. This is why physicians need to change the physical facilities in their offices on the days they see adolescents; this is why the facilities for adolescents in a children's hospital should be kept separate from those of the smaller children.

A fourth characteristic is their capacity and need for tremendous activity. They have a large amount of energy which needs acceptable channeling. Athletics is a very useful outlet for expending this energy, and we need to keep this in mind when we restrict their activity. If a medical indication for restriction arises, it is necessary to explain why they have to be restricted, to give some idea of when the restrictions may be lifted, and, if possible, substitute something in place of the outlet which has been taken away from them.

Another characteristic of adolescents is hero worship. They need, and are quite prone to find, adults for hero worship. We see this in girls with pictures of movie stars and boys with pictures of athletes plastered all over the wall. The physician historically has had a prestigious aura about him. The combination of prestige associated with the doctor plus a kindly interest in adolescents will engender considerable hero worship on the part of the adolescent. The wise physician can use this hero worship to advantage in whatever maneuvers are necessary in handling these young people. This trait, if properly used by the physician, can be a very valuable aid in whatever maneuvers he needs to use in the handling of his patient.

A sixth trait of this age group is that of rebellion. This is so characteristic that we become concerned if adolescents do not show at least a mild form of rebellion. Physicians should keep this in mind in handling them, particularly in being authoritative without being dictatorial, in being firm and understanding without being dogmatic. Adolescents resent dogmatism, and resent anyone, whether parents, teachers, or physicians, who try to mold them into something that they do not understand or do not want.

The outpatient department devoted to medical care of the adolescent needs to be, and has been in most hospital adolescent units in existence today, set up with the philosophy of being a general medical clinic. There the patient and physician meet for the first time, and the same patient and same physician, insofar as possible, stay as one unit just as long as the patient remains in the hospital. It is quite obvious that, in the face of the rapid expansion of medical knowledge, the physician can only skim the rapidly accumulating knowledge. The generalist who staffs the general medical clinic will need the consultant, whether cardiologist, neurologist, psychiatrist, renal physiologist, gynecologist, or orthopedist. These men act as both teachers and consultants; they attend the clinic on a given day when both patient and his doctor are present. The patient therefore has the benefit of the consultant's experience, and the physician the benefit of his teaching. If the problem is more difficult and the specialist feels that it can still be handled in the general medical clinic, it is then carried out under his direction. The adolescent with a more serious or exotic medical disorder will be better cared for by the specialist, as, for example, the patient who needs surgery or has a major emotional disorder. The above concept attempts to change the tendency in the past to treat the general medical clinic merely as a clearing station where patients are seen once and shunted off to a specialist.

Adolescents comprise, by and large, a healthy age group; the mortality rate is fairly low. Thus, in 1955, in the age group of ten to fourteen, there were approximately 6,300 deaths. Of these, almost half were due to accidents, and 988 due to automobile accidents. From age fifteen to nine-

teen, there were 10,000 deaths, of which almost 6,000 were due to accidents: the death rate from automobile accidents has risen sharply. This obviously has certain implications for preventive measures. The three major medical causes of death in this age group were: neoplasms, cardiovascular-renal disorders and cardiovascular disease, which accounted for some 2,500 deaths.[4]

Table 1 is reproduced from a paper by Williams,[5] and represents the experience of the Adolescent Clinic in Boston. This is a tabulation of all the new patients he saw during a two year period. The data, in part, are biased since there were certain units of the hospital which were known to the community as areas of unusual competence; most patients attending these clinics went through the Adolescent Medical Clinic prior to being admitted.

It is interesting to note that there were 427 patients whose disorders were primarily physical. It is of considerable interest that epilepsy and mental retardation were first and second in order of frequency.

Table 2 indicates that 323 patients were felt to have primarily functional conditions. One third of this group were labeled "Adjustment Reactions of Adolescence." This is a term which encompasses those adolescents who have a temporary emotional upheaval which is managed by a physician, and does not need psychiatric service. It is the patient, understanding physician who seems to act as a catalyst in restoring the

TABLE 1

Primarily Physical Conditions Observed in 750 Consecutive Patients at the Adolescent Unit, Children's Medical Center, Boston, Jan. 1956–Aug. 1958[5]

Diagnosis	Number of Patients		
	Girls	Boys	Total
Seizures	22	52	74
Mental retardation	16	45	61
No abnormality	13	48	61
Growth and development problems	19	33	52
Cardiac conditions	11	29	40
Miscellaneous conditions	9	22	31
Orthopedic problems	5	24	29
Ear, nose, throat and respiratory problems	9	15	24
Skin disorders	11	14	25
Brain damage	0	13	13
Speech disorders	1	8	9
Gynecological conditions	8	0	8
Total	124	303	427

TABLE 2

Primarily Functional Conditions Observed in 750 Consecutive Patients at the Adolescent Unit, Children's Medical Center, Boston, Jan. 1956–Aug. 1958[5]

Diagnosis	Number of Patients		
	Girls	Boys	Total
Adjustment reactions of adolescence	22	92	114
Neuroses	25	39	64
Behavioral problems	14	44	58
School problems	3	50	53
Psychoses	3	20	23
Enuresis	2	9	11
Total	69	254	323

emotional stability of these patients. The readiness of the adolescent to attach himself to a suitable adult model and the elasticity of his personality seem to allow this catalytic activity to take place readily.

Finally, it would be well to emphasize that those of us who devote our full-time medical thoughts and activities to this age group do not condone adolescence as a specialty. However, we do feel that there should be training units in the major teaching centers of the country so that the available knowledge of this age group may diffuse into general medical education. In addition, it offers the opportunity to further our knowledge of the adolescent's physiological and psychological characteristics; with increased knowledge, diseases of adolescents and their reaction to illness are better understood and treated.

Dr. J. Roswell Gallagher, who has pioneered in the field of adolescent medicine, has most aptly summarized the need for increased emphasis on this age group:[6]

> We all need to know more about adolescents. They are, after all, the adults of tomorrow, the inheritors of our civilization. Those who are now handicapped, or whose personalities and future effectiveness and happiness are threatened, have still the hope of change for the better. Later, and soon, that malleability, that capacity for change will be largely lost. Adolescence is the latest of the age periods in which we can expect success from other than the most expert and the most prolonged efforts to strengthen personalities or to build emotional or physical health.

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Hypertonic Dehydration

Leonard B. Berman, M.D.*

Hypertonic dehydration is a particularly interesting condition, the pathophysiology and clinical picture of which are considerably different from those of the more usual dehydration. The study of hypertonic dehydration offers a unique opportunity to consider some of the physicochemical relationships of body water and solute, and the clinical consequences of these relationships. In this connection, the concepts which underlie the terms *osmotic pressure* and *hypertonic* require some brief comment.

In the classical student experiment, an aqueous solution of sugar is placed in a bag, the wall of which is impermeable to the sugar, and immersed in water; the water moves from the outside into the bag. Water never moves without some force or pressure to drive it, and in this case osmotic pressure has been demonstrated; the amount of pressure is directly proportional to the moles of glucose present. The same phenomenon obtains with body fluids. When water moves between extracellular fluid and intracellular fluid, it does so by virtue of osmotic pressure differences. Water will move from the area of lower osmotic pressure to the area of higher until the pressures are equal.

Clinicians use the word tonicity to refer to solutions as hypertonic, isotonic, and hypotonic. Tonicity, in this sense, compares the osmotic pressure of a solution to that of body fluids. The water in plasma, in cells, and interstices has an osmotically active solute content equivalent to approximately 300 milliosmols per liter; a solution with an osmotic

* Consulting Staff, Children's Hospital; Chief and Program Director, Renal Diseases Research and Training, Children's Hospital Research Foundation; Assistant Professor of Medicine, Georgetown University School of Medicine.

pressure of 300 milliosmols per liter is, therefore, termed isotonic. Hypertonic and hypotonic solutions have an osmotic pressure of more than 300 and less than 300 milliosmols per liter respectively. The number of milliosmols per liter in a solution depends on the nature of the solute and its concentration. In the human body, extracellular fluid has sodium and accompanying anion dissolved in it. The sodium salts are at such a concentration that the osmolarity of extracellular fluid is about 300 milliosmols per liter. On the other side of the cell membrane, in the cell, the major substances are potassium, phosphate and protein; intracellular fluid also has a concentration of 300 milliosmols per liter. This is the normal state and creates no net movement of water across the cell membrane; the extracellular and intracellular compartments, therefore, maintain a constant volume. It is important to note that impermeability of the membrane to a solute needs to exist in order to create an effective gradient of osmotic pressure. If the concentration of extracellular solute (e.g. sodium) changes, the osmotic pressure of the extracellular fluid will change, and water must move.

The cations of extracellular fluid include sodium, potassium, calcium, and magnesium; the anions include chloride, bicarbonate, and protein. Of all these, sodium is quantitatively the most important and *it is the only one whose change will significantly change the total concentration of solute.* For example, in a child with respiratory acidosis who has decreased his serum chloride concentration considerably, there is no change in serum osmolarity because, in this situation, bicarbonate has risen to fill the gap. The characteristic serum pattern is a high carbon dioxide combining power, a low chloride, and a normal sodium; the total osmotic pressure, however, is identical to that which existed before the abnormality. This illustrates that changes in chloride and bicarbonate may often be reciprocal and need not affect osmolarity.

Potassium, calcium, and magnesium are other important constituents of serum. Their changes have great clinical significance but the concentrations are so small that osmotic pressure cannot be much affected. Sodium is the one substance present in sufficiently large amounts that changes in its concentration are difficult to compensate. If the sodium level falls to 120 milliequivalents per liter, osmotic pressure will decrease by 20 milliequivalents per liter or 40 milliosmols per liter. In this condition, hyponatremia, water must move from extracellular fluid to intracellular fluid, i.e. from the region of lower osmotic pressure to the higher.

The condition known as hypertonic dehydration represents the opposite situation. When the concentration of serum sodium rises above normal, the osmotic pressure of extracellular fluid rises and brings forth water from cells. If extracellular fluid contains sodium at 160 milliequivalents per

liter the osmolarity has increased to 320 milliosmols per liter, and intracellular water containing only 300 milliosmols per liter must move across the cell membrane. An elevated serum sodium, therefore, is synonymous with hyperosmolarity.

There are definite clinical syndromes which may result in a high concentration of serum sodium. The one easiest to understand occurs when access to water is totally cut off. This may occur, for example, to an adult who lives alone and has suffered some kind of illness, e.g., a stroke, and simply is unable to get to a source of water. It might occur to a psychotic person who cannot make his desire for water known. It might happen to an infant who is either abandoned or neglected. All of these patients are taking in no water but are constantly losing water via the skin, lungs, and urine. The urine volume can be decreased, but not the skin and lung losses. In the infant, these losses are considerably higher per Kg. of body weight than in the adult. The water lost via the skin and lungs contains no solute. It is literally distilled water, and thus quite different from sweat. The patient losing water without concomitant sodium loss develops a high concentration of sodium in his blood, a hyperosmolarity of his extracellular fluid, and therefore a movement of water from the cells. In the patient whose serum sodium is 160 milliequivalents per liter, water has already moved from the cells into the extracellular fluid, leaving a relatively higher osmolarity in the intracellular fluid; osmotic equality is present again but at a higher level.

This lack of access to water is called the desiccation syndrome. The diagnosis is usually a matter of the history. What were the circumstances surrounding the child's illness? What was he given to drink? Was it possible, for example, that, by mistake, all water was withheld? Fever increases the loss of water from skin and lungs; therefore, the febrile child without access to water is more liable to the desiccation syndrome.

The desiccation syndrome has, by far, the clearest pathogenesis of hypernatremia. In another type of disorder, the cause is harder to explain; this is the child with diarrhea who has hypernatremia. Here, it may be quite difficult to understand why the serum sodium concentration is elevated. Diarrhea fluid and gastric juice alike contain a concentration of sodium greatly below that of blood (30 to 60 milliequivalents per liter). If a dilute sample of any solution is removed, the original fluid is left more concentrated than before. If the patient is vomiting or has diarrhea, he is losing a dilute sample from his extracellular fluid; this should raise his serum sodium. This seldom happens; in fact such a patient almost always has a lower than normal serum sodium. This means, obviously, that extracellular fluid is not a closed system. Water and sodium are appearing and disappearing in accordance with many influences, so that it cannot

be predicted from what is being lost what the concentration will be in the remaining body fluids.

Most children with diarrhea are hyponatremic; only occasinally does hypernatremia occur, even though it would seem to be a more likely possibility. We are forced, thus, into other considerations. According to one theory, the level of osmotic pressure in body water is set at any given level by the so-called "osmostat" somewhere in the brain. For example, if by drinking a glass of water the osmotic pressure of the blood is lowered even slightly, the "osmostat" will record it, the amount of urine water will increase, and the osmotic pressure of the blood will return to normal.

The normal "osmostat" is set at about 300 milliosmols per liter (140 mEq./L. of sodium). However, if the brain is not functioning properly, the excretion of water may change sufficiently so that hypernatremia results. Children with diarrhea who become hypernatremic are usually not the most dehydrated children; they may be moderately or even only mildly dehydrated. It has been suggested that the diarrheal syndrome which produces this is, in fact, a diffuse syndrome affecting the brain, the meninges and the gastrointestinal tract. The speculative nature of this explanation is easily appreciated.

Other children with diarrhea may be given electrolyte replacement by mouth; the most common preparation, when made up as the manufacturer advises, should furnish 50 milliequivalents per liter of sodium. Yet many children who are given such a hypotonic mixture show hypernatremia. What this must mean is that the body does not properly choose how much of each it will keep and so retains too little water and too much sodium. Hyperosmolarity results.

There are at least two more conditions causing hypernatremia. One occurs in the child with diabetes insipidus whose urine volumes are huge and consist almost entirely of water; this child is analogous to the child whose access to water is cut off and who continues to lose water from the skin and lungs.

Finally there is the peculiar syndrome of solute loading, with particular reference to protein and, therefore, to urea. A child who is being given large amounts of protein, and therefore is producing large amounts of urea, is forced to excrete very large volumes of salt-poor urine, just as the child with diabetes insipidus. In adult medicine this syndrome is produced in the comatose patient with the stomach tube into which large amounts of protein hydrolysate, amino acids, milks, etc. are poured. It has also been described in children given unmodified cows' milk, with its relatively large protein load.

Clinically, all the above circumstances have in common dehydration. Is there anything characteristic about hypertonic dehydration? First,

water has been forced to come out of cells, partially to replace the missing extracellular fluid. This means that a hypertonically dehydrated child will show much less clinical dehydration than would be expected for a given amount of water deficit.

Another frequently described characteristic of the clinical syndrome of hypertonic dehydration is the central nervous system signs. There are a number of studies in animals and humans which demonstrate that hyperosmolarity of extracellular fluid leads to a very low cerebral spinal fluid pressure, capillary dilatation and rupture, hemorrhages on the surface of the brain, subdural effusions, and meningismus. The reasons are not clear. It is said that the brain acts differently from other organs with regard to giving up water or taking on sodium.

The diagnosis of hypertonic dehydration is easily made by the laboratory, since the normal serum sodium concentration in children is close to that of adults, i.e., 135 to 145 milliequivalents per liter.

The treatment of hypertonic dehydration differs from the treatment of isotonic or hypotonic dehydration. The primary interest is in lowering osmotic pressure rather than replacing a deficit of sodium, if one exists. This is a good example of a situation in which the serum concentration of a cation is not correlated with the total body store of that cation. There may be a modest deficit, for example, of total body sodium in spite of the high serum concentration.

There is general agreement on the need for water, but there is controversy whether the water should contain some sodium or only sugar since convulsions are not infrequently seen during early treatment. It has been suggested by those who recommend giving sodium that these convulsions are due to a too rapid change of osmotic pressure; obviously, if water alone is given the change is more rapid than that with water and sodium. An opposing theory is that these convulsions are due to the underlying hypernatremia; it must be said for this theory that convulsions do occur before treatment as well as during treatment. A compromise solution is water with 20 milliequivalents of sodium per liter added. The amount of water to be given is calculated exactly as it is calculated in any dehydrated child, i.e., estimating the total deficit in terms of body weight, plus the current insensible loss based on surface area, plus the amount of continuing losses.

The child with hypernatremia has two other associated laboratory findings on occasion: a low calcium and a low potassium. The reasons for this are unclear, but it is accepted practice to administer 20 to 30 ml. of 10 per cent calcium gluconate and to replace the potassium as with any dehydrated child, 3 milliequivalents per Kg. of body weight given the first day of treatment.

Lumbar punctures are often performed because of the clinical manifestations, i.e., signs of meningitis and signs of increased intracranial pressure. Subdural effusions, if present, are treated conservatively.

SUMMARY

Hypertonic dehydration is present when the osmotic pressure of body water rises above 300 milliosmols per liter. This may be simply diagnosed by the presence of an elevated serum sodium concentration. The pathogenesis includes lack of access to water, abnormally large volumes of dilute urine, and certain types of gastrointestinal fluid losses. The clinical picture may be characterized by central nervous system signs and an absence of the findings of severe dehydration, even though the water deficit is large. Treatment consists of water containing a small concentration of sodium. The amount of water given in the first 24 hours should be equal to the sum of maintenance requirements and estimated deficit.

The Editor's Column

Physicians and Sociology

The 1960 White House Conference on Children and Youth

Of 670 recommendations that resulted from the recent White House Conference on Children and Youth, only 24, or 4 per cent, dealt with medical problems of children, and those centered around the need for periodic health examinations, reduction of neonatal morbidity and mortality, and education in regard to proper nutrition. The majority of recommendations from this five day conference, which included eminent pediatricians as well as other physicians, had to do with concerns about housing, family disorganization, city planning, education, religion, and the integration of children with various disabilities into the educational system and work force.

It is noteworthy that a conference whose purpose was "to promote opportunities for children and youth to realize their full potential for a creative life in freedom and dignity" contained so little about the medical needs of youngsters. This is no criticism of the conference, but an attempt, however gross, to take the pulse of the interests and concerns of a group that is certainly among the most significant in the area of the welfare of

children. The themes of the conference's recommendations emphasize how far we have come from the time of Sir William Osler's statement that "Humanity has but three great enemies: fever, famine and war; of these by far the greatest, by far the most terrible, is fever."

The conference was organized about a number of keynote speeches; these were followed by small workgroups which drafted recommendations. The speeches underlined concerns about family solidarity, the impact of technology and mass media, moral weakness, and the problems of minority groups. The workgroups, very much in the spirit of the times, recommended research and Federal aid as the most relevant action toward understanding and dealing with these problems.

The recommendations of this conference, reflecting the conclusions of a number of recent meetings in which pediatricians participated, add force to the call for knowledgeability in the sociological and psychological disciplines. One way of learning something about these disciplines is by reading the three informative, concisely written paperback volumes of policy and background papers published for the conference.[1, 2] Change, as always, is upon us, and the demand for revision of our concepts of child care becomes an ever more insistent one. The pediatrician, because of his unique relationship to the family and the community, has the privilege to follow and help direct these changes occurring in health practices, if he is prepared to do so.

SIDNEY L. WERKMAN, M.D.

REFERENCES

1. The Nation's Children, ELI GINZBERG, Editor, 3 volumes, New York, Columbia University Press, 1960.
2. Children and Youth in the 1960's (30 survey papers), Department of Health, Education and Welfare, Washington, D. C.

Book Reviews

The Development of the Infant and Small Child, Normal and Abnormal. By R. S. ILLINGWORTH, 326 pages, 95 illustrations, Edinburgh and London: E. & S. Livingstone, Ltd., 1960. The Williams & Wilkins Co. Baltimore, exclusive U. S. Agents, $6.50.

This is a unique book—its counterpart does not exist on this side of the Atlantic Ocean. This fact is not really very surprising when it is recognized that few, if any, American physicians have the author's wide interest in,

knowledge of, and experience with, mentally and neurologically handicapped children. Dr. Illingworth, who is Professor of Child Health at the University of Sheffield, might very well go under the title of "Mr. Handicapped Child." It is practically impossible, for example, to read any issue of the British pediatric journal, Archives of Diseases in Childhood, without finding a very carefully and thoughtfully written article authored or co-authored by Dr. Illingworth.

This reviewer has often wondered that it took so long for somebody to write this book; it fills a real need—information gathered together in this very concisely and compactly written volume is otherwise available only from very widespread sources. Its general plan represents in the main: 1) an extensive literature review of what others have discovered, 2) a strong plug for the Gesell method of assessing early development (and incidentally, reiterating what Gesell *really* said rather than what has been attributed to him), and 3) a compendium of the author's impressions and experience in a long career in dealing with handicapped children. It should be mentioned that the title of the book is misleading since it deals *only* with the mental and neuromuscular growth of the child, and contains no information whatsoever on the physical growth of the child.

The author states the theme of the book on page 8 when he quotes Dr. Arnold Gesell: "By methods of developmental diagnosis *supplemented with clinical experience*, it is possible to diagnose in the first year of life nearly all causes of amentia, of cerebral injury, many sensory and motor defects, and severe personality deviations" (reviewer's italics). Further the author stresses his belief (originally Gesell's) that a book on child development can rightly be written only by a pediatrician since this is the one profession with the background and training not only to assess properly the current mental and neuromuscular status but also to evaluate both historical and current environmental factors which enter into the total evaluation of the child.

Much of the early portion of this book is devoted to a presentation of the pros and cons of the controversy concerning the predictive values of developmental assessment in infancy; my consultant psychologist informs me that both sides are presented very fairly and clearly. Dr. Illingworth, however, leaves no doubt as to which side he favors—one of his major points is that the majority of research workers who believe that early developmental assessment has rather limited predictive value *have excluded the very children in their studies in whom such assessment would be most useful, i.e., the mentally retarded and neurologically disabled.*

It is not difficult to believe, and the author so states, that he is a disciple of Gesell. Two of the middle chapters of the book are the author's attempt to apply Gesell's studies to everyday pediatric practice, using a minimum

of equipment and without special training. These chapters contain a large number of very valuable photographs illustrating various developmental stages in the first two years of life which add immeasurably to the value of this section. Dr. Illingworth stresses the need for repeated examinations and places heavy emphasis on such factors as alertness, responsiveness, interest in surroundings, vocalizations and powers of concentration which are very difficult to score and are usually ignored. Who better than the physician seeing children as part of routine well-baby care to evaluate these factors?

But this is only a portion of the book. The chapter on prenatal and perinatal factors capable of affecting neuromuscular and mental development is the most complete this reviewer has ever seen in one place (106 references); another chapter discusses and describes in very complete fashion the association of mental deficiency with various disease states and conditions (162 references) and is almost worth the price of the book itself. There are, in addition, chapters on the early diagnosis of mental deficiency and cerebral palsy, a chapter on mental superiority and several very valuable chapters documenting variations in the different *fields* of development (walking, talking, etc.) and variations in the *general pattern* of development. Another chapter is devoted to a discussion of environmental factors affecting mental development, including the effects of environmental deprivation.

Dr. Illingworth's style is frequently narrative; while this makes the book easy to read, it detracts from its organization. Repetitions abound (this is not necessarily a disadvantage) and odd bits of material are sometimes tucked in unusual places. He also has the exasperating habit of presenting the literature in great detail and then offering an "off the top of the head" opinion without indication of any personal data to back it up. These defects, however, are of a minor nature.

This indeed is a very personal book, frequently stating only the author's observations and opinions, but written by a man whose background and experience eminently qualify him to do so. The book is recommended without reservation to anyone interested in the developmental problems of infancy and childhood: medical student, resident, pediatrician, general practitioner, neurologist, psychiatrist, and psychologist.

J. WILLIAM OBERMAN, M.D.

Symposium on Glaucoma. Edited by WILLIAM B. CLARK, M.D., 314 pages, 99 figures including 2 in color, St. Louis: The C. V. Mosby Company, 1959, $13.50.

In this symposium, various features of the glaucomas are considered in 21 chapters and an appended round table discussion. Since the text deals

mainly with recent studies and such material is clearly presented, this book is an excellent source of information about disorders of ocular pressure control.

There are two very good chapters concerning the effects of glaucoma on ocular structure and function by Theobald. These, and the discussion of visual field changes by Hass, provide valuable instruction on the nature of the disease for all readers. Of particular importance is the emphasis given to the recommendation that visual field studies be done or requested in screening for glaucoma.

Five chapters on operative treatment are of special interest to ophthalmology. Opinions on the role of surgery are moderate, and there is frank admission of the limitations in operative management of glaucoma; this trend is welcome. One would like to have seen, in addition, more follow up and control data included among the operative results discussed.

Research studies in glaucoma (i.e., aqueous humor dynamics and histochemical studies) are reported concisely and are well illustrated. Workers desiring a more comprehensive treatment will prefer the Macy Foundation Reports, 1955–59.

Pediatricians will have special interest in the discussion of the nature and treatment of congenital glaucoma, which is presented from several points of view.

Taken over-all, the symposium represents a necessary presentation of latest thinking in a rapidly changing field.

J. O'Rourke, M.D.

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